Medical Genetics Summaries on the NCBI Bookshelf:
a pharmacogenomics resource for clinicians

NCBI Webinars

- Closed captioning: www.captionedtext.com and enter 3239619
- The **recording**, will be on our YouTube channel in the Webinars playlist: <youtube>/user/NCBINLM/playlists
- Use the Q&A pod to ask questions when you think of them. Don't wait until the end.
- Answers available after the webinar linked to our Webinars page: <ncbi>/home/coursesandwebinars.shtml
- Materials / Q&A: http://go.usa.gov/xXS6W

04/26/2017

Medical Genetics Summaries on the NCBI Bookshelf:
a pharmacogenomics resource for clinicians

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Each chapter describes information about a drug, known impacts of genetic variation on drug response (eg. efficacy, toxicity, side effects) and actionable information (eg. relevant genetic testing, how to interpret test results to optimize therapy)

4/26/2017

Medical Genetics Summaries (MGS)

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Concise reviews about genetic variation and drug responses, accessible at the point of care

- Created by NCBI
- Peer reviewed
- Updated every 2-3 years or if new guideline is released
- Freely available from NCBI Bookshelf: https://www.ncbi.nlm.nih.gov/books/NBK61999/
- Downloadable as PDF
- Links to/from other NCBI resources: GTR, MedGen

Standardized format

Abacavir Therapy and *HLA-B*57:01* Genotype

Laura Dean.

Created: September 1, 2015.

Drug: Abacavir

Gene: *HLA-B*57:01*

Genetic Testing

Therapeutic Recommendations based on Genotype

Nomenclature

NCBI Bookshelf:
https://www.ncbi.nlm.nih.gov/books/NBK61999/

What is in MGS?

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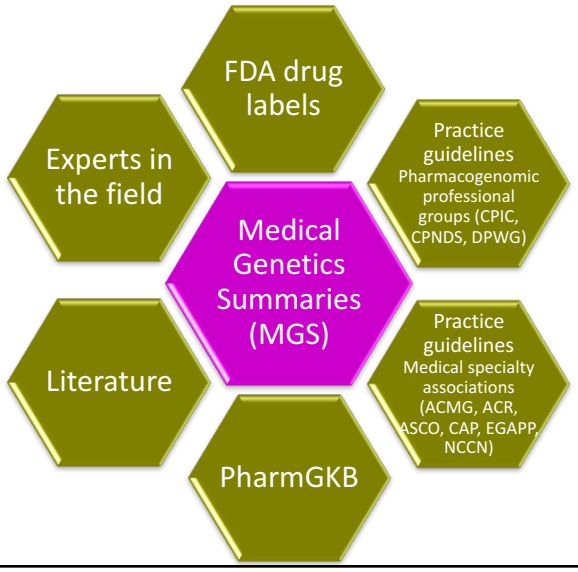

How to access the MGS

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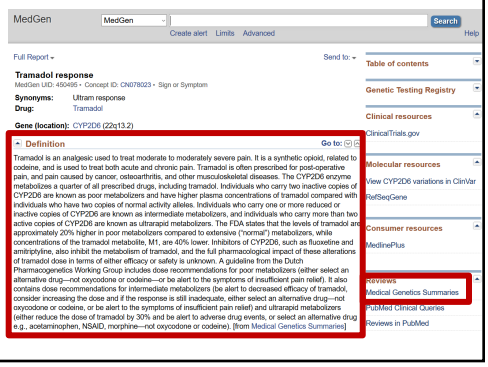
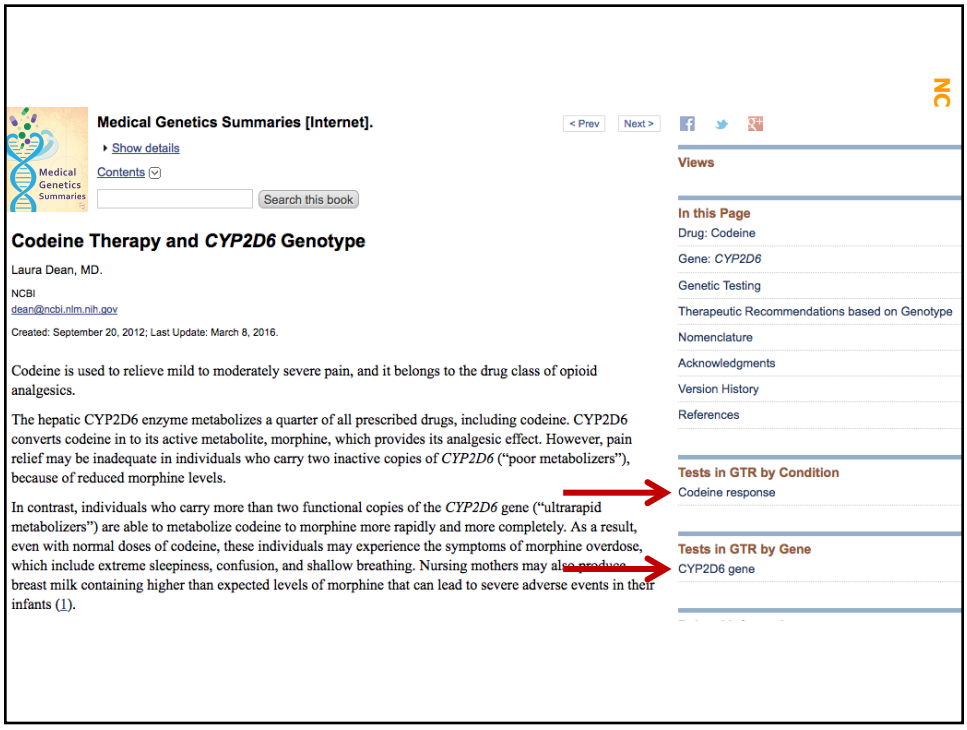
GTR - database of orderable clinical and research genetic tests: www.ncbi.nlm.nih.gov/gtr/

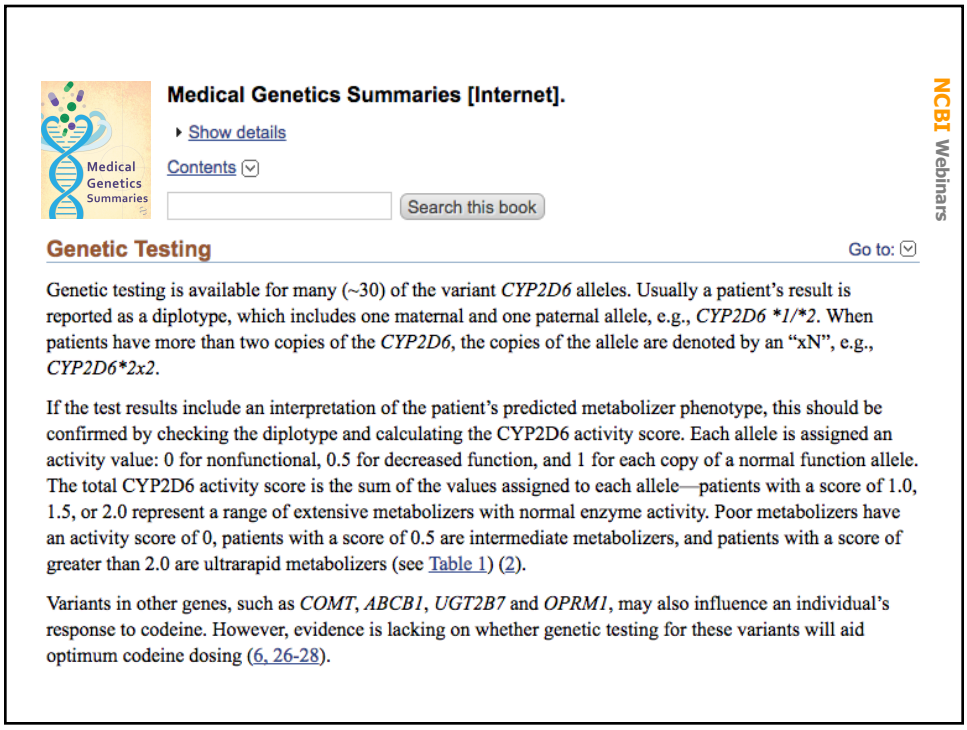
MedGen - portal to information about phenotypes with a genetic component: www.ncbi.nlm.nih.gov/medgen/



MGS articles: Genetic variants and drug responses

- Abacavir Therapy and *HLA-B*57:01* Genotype
- Allopurinol Therapy and *HLA-B*58:01* Genotype
- Amitriptyline Therapy and CYP2D6 and CYP2C19 Genotype
- Aripiprazole Therapy and *CYP2D6* Genotype
- Atomoxetine Therapy and *CYP2D6* Genotype
- Azathioprine Therapy and *TPMT* Genotype
- Capecitabine Therapy and *DPYD* Genotype
- Carbamazepine Therapy and *HLA* Genotypes
- Carisoprodol Therapy and CYP2C19 Genotype
- Celecoxib Therapy and *CYP2C9* Genotype
- Clopidogrel Therapy and *CYP*2C19 Genotype
- Clozapine Therapy and *CYP2D6*, *CYP1A2*, and *CYP3A4* Genotypes
- Codeine Therapy and *CYP2D6* Genotype
- Diazepam Therapy and *CYP2C19* Genotype
- Esomeprazole Therapy and *CYP2C19* Genotype
- Fluorouracil Therapy and *DPYD* Genotype
- Gentamicin Therapy and *MT-RNR1* Genotype
- Imipramine Therapy and CYP2D6 and CYP2C19 Genotype
- Irinotecan Therapy and *UGT1A1* Genotype
- Maraviroc Therapy and *CCR5* Genotype
- Mercaptopurine Therapy and *TPMT* Genotype
- Metoprolol Therapy and CYP2D6 Genotype
- Omeprazole Therapy and *CYP2C19* Genotype
- Pertuzumab Therapy and *ERBB2* (*HER2*) Genotype
- Phenytoin Therapy and *HLA-B*15:02* and *CYP2C9* Genotypes
- Prasugrel Therapy and CYP Genotype
- Propafenone Therapy and CYP2D6 Genotype
- Risperidone Therapy and CYP2D6 Genotype
- Simeprevir Therapy and *IFNL3* Genotype
- Sofosbuvir Therapy and IFNL4 Genotype
- Tamoxifen Therapy and *CYP2D6* Genotype
- Thioguanine Therapy and *TPMT* Genotype
- Thioridazine Therapy and CYP2D6 Genotypes
- Tramadol Therapy and *CYP2D6* Genotype
- Trastuzumab Therapy and *ERBB2* (*HER2*) Genotype
- Venlafaxine Therapy and *CYP2D6* Genotype
- Warfarin Therapy and the Genotypes *CYP2C9* and *VKORC1*




Medical Genetics Summaries
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Show details
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Genetic Testing
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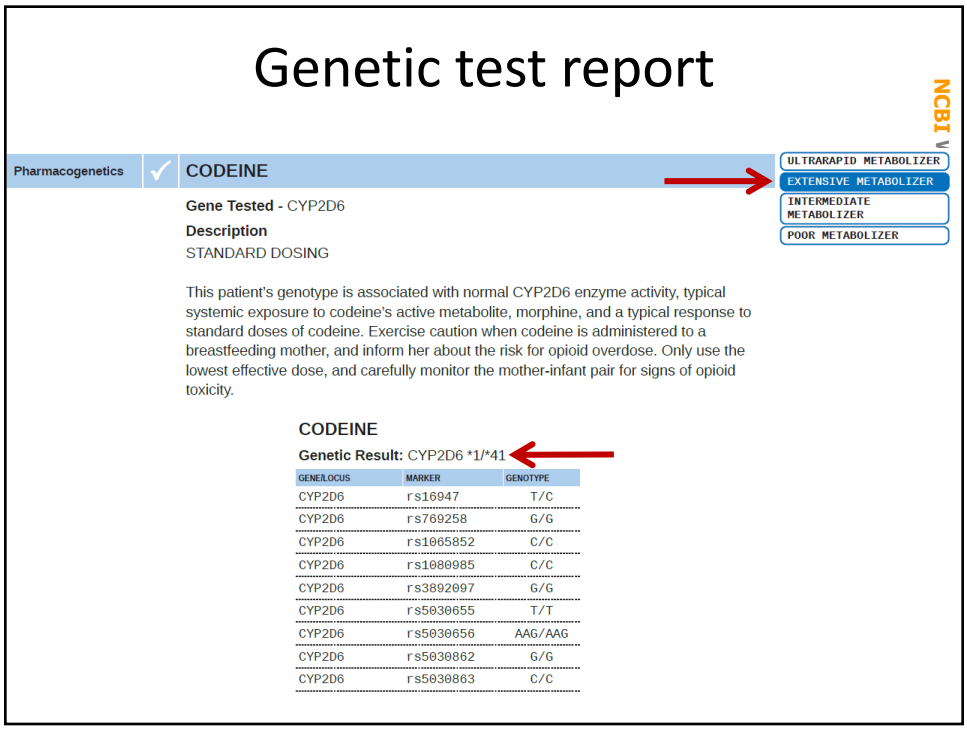
Genetic testing is available for many (~30) of the variant CYP2D6 alleles. Usually a patient's result is reported as a diplotype, which includes one maternal and one paternal allele, e.g., CYP2D6 *1/*2. When patients have more than two copies of the CYP2D6, the copies of the allele are denoted by an "xN", e.g., CYP2D6*2x2.
If the test results include an interpretation of the patient's predicted metabolizer phenotype, this should be confirmed by checking the diplotype and calculating the CYP2D6 activity score. Each allele is assigned an activity value: 0 for nonfunctional, 0.5 for decreased function, and 1 for each copy of a normal function allele. The total CYP2D6 activity score is the sum of the values assigned to each allele—patients with a score of 1.0, 1.5, or 2.0 represent a range of extensive metabolizers with normal enzyme activity. Poor metabolizers have an activity score of 0, patients with a score of 0.5 are intermediate metabolizers, and patients with a score of greater than 2.0 are ultrarapid metabolizers (see Table 1) (2).
Variants in other genes, such as COMT, ABCB1, UGT2B7 and OPRM1, may also influence an individual's response to codeine. However, evidence is lacking on whether genetic testing for these variants will aid optimum codeine dosing (6, 26-28).


Genetic test report
NCBI
Pharmacogenetics
CODEINE
ULTRARAPID METABOLIZER
EXTENSIVE METABOLIZER
INTERMEDIATE METABOLIZER
POOR METABOLIZER
Gene Tested - CYP2D6
Description
STANDARD DOSING
This patient's genotype is associated with normal CYP2D6 enzyme activity, typical systemic exposure to codeine's active metabolite, morphine, and a typical response to standard doses of codeine. Exercise caution when codeine is administered to a breastfeeding mother, and inform her about the risk for opioid overdose. Only use the lowest effective dose, and carefully monitor the mother-infant pair for signs of opioid toxicity.
CODEINE
Genetic Result: CYP2D6 *1/*41
GENE/LOCUS MARKER GENOTYPE
CYP2D6 rs16947 T/C
CYP2D6 rs769258 G/G
CYP2D6 rs1065852 C/C
CYP2D6 rs1080985 C/C
CYP2D6 rs3892097 G/G
CYP2D6 rs5030655 T/T
CYP2D6 rs5030656 AAG/AAG
CYP2D6 rs5030862 G/G
CYP2D6 rs5030863 C/C

Allele nomenclature

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Common allele name	Alternative names	HGVS reference sequence		dbSNP reference identifier for allele location
		Coding	Protein	
*CYP2D6*4*	1846G>A	NM_000106.4:c.506-1G>A	Not applicable - variant occurs in a non-coding region	rs3892097
*CYP2D6*5*	Not applicable - variant results in a whole gene deletion			
*CYP2D6*6*	1707 del T Trp152Gly	NM_000106.4:c.454delT	NP_000097.2:p.Trp152Glyfs	rs5030655
*CYP2D6*10*	100C>T Pro34Ser	NM_000106.4:c.100C>T	NP_000097.2:p.Pro34Ser	rs1065852
*CYP2D6*17*	Includes*: 1023C>T (Thr107Ile) 2850C>T (Cys296Arg)	NM_000106.4:c.320C>T NM_000106.4:c.886T>C	NP_000097.2:p.Thr107Ile NP_000097.2:p.Cys296Arg	rs28371706 rs16947
*CYP2D6*36*	Includes: 100C>T (Pro34Ser) 4180G>C	NM_000106.4:c.100C>T NM_000106.5:c.1457G>C	NP_000097.2:p.Pro34Ser NP_001020332.2:p.Ser435Thr	rs1065852 rs1135840
*CYP2D6*41*	2988G>A	NM_000106.4:c.985+39G>	Not applicable – variant occurs in a non-coding region	rs28371725

Activity status of relevant alleles

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Activity status of selected ***CYP2D6*** alleles

Allele type	*CYP2D6* Alleles
Normal function	**1*, **2*, **33*, **35*
Decreased function	**9*, **10*, **17*, **29*, **41*
No function	**3*-**8*, **11*-**16*, **19*-**21*, **38*, **40*, **42*

For a detailed list of ***CYP2D6*** alleles, please see (18).

Codeine therapy recommendations based on CYP2D6 phenotype, adapted from CPIC

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Phenotype	Activity score	Phenotype details	Genotype	Examples of diplotypes	Recommendations for codeine therapy[1]	Considerations for alternative opioids
Ultrarapid metabolizer (approximately 1–2% of patients)	Greater than 2.0	Increased enzyme activity. Increased formation of morphine following codeine administration, leading to higher	More than two copies of normal function alleles	*1/*1xN *1/*2xN	Avoid codeine use due to potential for toxicity.	Alternatives that are not affected by this CYP2D6 phenotype include morphine and non-opioid analgesics. Tramadol and, to a lesser extent, hydrocodone and oxycodone are not good alternatives because their metabolism is affected by CYP2D6 activity.
Normal metabolizer (approximately 77–92% of patients)	1.0-2.0*	Normal enzyme activity. Normal morphine formation.	Two normal function alleles, or two decreased function alleles, or one normal function allele and one decreased or no function allele, or combinations of duplicated alleles that result in an activity score of 1.0 to 2.0	*1/*1 *1/*2 *2/*2 *1/*41 *1/*4 *2/*5 *1/*10	Use label-recommended age- or weight-specific dosing.	
Intermediate metabolizer (approximately 10–15% of patients)					alternative analgesics such as morphine or a nonopioid.	
Poor metabolizer (approximately 5–10% of patients)	0	Low or absent enzyme activity. Greatly reduced morphine formation following codeine administration, leading to insufficient pain relief.	Two no function alleles	*4/*4 *4/*5 *5/*5 *4/*6	Avoid codeine use due to lack of efficacy.	Alternatives that are not affected by this CYP2D6 phenotype include morphine and non-opioid analgesics. Tramadol and, to a lesser extent, hydrocodone and oxycodone are not good alternatives because their metabolism is affected by CYP2D6 activity; these agents should be avoided.

* Activity scores are based on the formation of morphine from codeine. Other investigators may define normal metabolizers with a score of 1.5-2.0, and intermediate metabolizers with a score of 0.5-1.0.

[1] The strength of therapeutic recommendations is "moderate" for intermediate metabolizers, and "strong" for all other metabolizers.

Table is adapted from Crews K.R. et al. Clinical Pharmacogenetics Implementation Consortium guidelines for cytochrome P450 2D6 genotype and codeine therapy: 2014 update. Clinical pharmacology and therapeutics. 2014;95(4):376-82 (2).

Therapeutic recommendations based on Genotype from authoritative sources

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Therapeutic Recommendations based on Genotype

This section contains excerpted[1] information on gene-based dosing recommendations. Neith
other parts of this review contain the complete recommendations from the sources.

2015 Statement from the US Food and Drug Administration (FDA) Respiratory depression a
occurred in children who received codeine in the post-operative period following tonsillectomy a
and had evidence of being u
isoenzyme 2D6 [CYP2D6]
exposed to high levels of m

Some individuals may be u
as *1/*1xN or *1/*2xN). Th
in Chinese and Japanese, 0.
North Africans, Ethiopians,
codeine into its active meta
results in higher than expec
rapid metabolizers may hav
extreme sleepiness, confusi

Please review the complet

2014 Statement from the Clinical Pharmacogenetics Implement

dose of codeine, as recommended in the product label, is warranted
phenotype (i.e., a CYP2D6 activity score of 1.0–2.0). Likewise, a s
patients with an intermediate metabolizer phenotype (i.e., activity s
closely for less-than-optimal response and should be offered an alte
substrate tramadol is selected as alternative therapy in intermediate
due to the possibility of poor response.

If clinical genotyping identifies a patient as a CYP2D6 poor metabo
supports the avoidance of codeine and the use of an alternative anal
an analgesic other than the CYP2D6 substrates tramadol, hydrocod
preferable. There is insufficient evidence in the literature to recomm
especially considering the evidence that select adverse effects do no
In a patient identified as a CYP2D6 ultrarapid metabolizer (i.e., acti
should be made to avoid the risk of severe toxicity with a "normal"

Please review the complete therapeutic recommendations that a

2013 Clinical practice Guideline from the "Canadian Pharmacogenomics Network for Drug Safety (CPNDS) Clinical Recommendations Group: *CYP2D6* genotyping for safe and efficacious codeine therapy":

1. Who should be tested and when?
   - Young children about to receive codeine for pain management and women about to receive codeine for postpartum pain while breastfeeding should be tested for CYP2D6 (Grade A – strong recommendation).
   - Children and adults who continue to have pain despite high doses of codeine should be tested for CYP2D6 (Grade B – moderate recommendation).
   - Genetic testing for CYP2D6 should be considered before administering codeine for the first time in all children and adults in order to rule out non-responders and to identify individuals who may be susceptible to adverse effects from codeine (Grade C – optional recommendation).
2. What gene variants should be tested?

Given the numerous polymorphisms in CYP2D6 and the diversity of the Canadian population, a full-scale analysis of both common and rare CYP2D6 variants is advised (Grade B- moderate recommendation)

- *CYP2D6* alleles with decreased or no function: *CYP2D6 *3 - 12, 14-15, 17, 19-20, 29, 40-42, 44, 49, 50, 54- 56, 59; *4XN, *10XN*
- *CYP2D6* alleles with normal or increased function: *CYP2D6 *2* (normal), **1XN* (increased), **2XN* (increased), **17XN, *35XN* (increased), **41XN*, in addition to *CYP2D6* copy number determination.

Recommendations: Genotype-Specific Treatment Options

- Poor metabolizers of CYP2D6 should not receive codeine for pain relief (Grade A- strong recommendation).
- Ultrarapid metabolizers of CYP2D6 should avoid codeine for pain relief and receive alternative analgesics that do not have potent CYP2D6 metabolites (Grade B- moderate recommendation).
- Certain populations, especially opioid naïve breastfed neonates of mothers with functional *CYP2D6* gene duplications taking codeine and young children may be particularly susceptible to codeine-induced central nervous system depression. Breastfeeding mothers and young children who are ultrarapid metabolizers of CYP2D6 should avoid codeine (Grade A – strong recommendation).
- In individuals with IM or EM *CYP2D6* genotypes, codeine can be used as per standard of care. Existing evidence suggests that caution is still warranted in *CYP2D6* EMs receiving codeine if they are receiving maximal therapeutic doses of codeine and have additional risk factors for toxicity.

How to incorporate NCBI resources in a clinical setting

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- Consider a differential diagnosis
- Find clinical, molecular & research info on a condition or phenotype
- Use links to relevant information

- Find a suitable test

How to incorporate NCBI resources in a clinical setting

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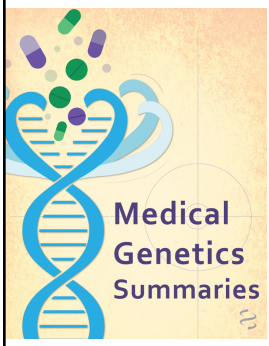
- Translate lab report into clinical action:



  - Therapeutic dosing recommendations by phenotype
  - Enzymatic activity status of significant alleles
  - Assignment of likely phenotype based on genotypes
  - Translate variant terms: HGVS, star allele, variant description from the literature, and dbSNP # (rsid)

MORE INFORMATION

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- https://www.ncbi.nlm.nih.gov/books/NBK61999/

NIH Genetic Testing Registry

- https://www.ncbi.nlm.nih.gov/gtr/

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